Redox Biology 38 (2021) 101831

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Commentary

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In our article [1], we supplemented melatonin to aged female mice to assess its impact on the oocyte quality especially the prevention of oocyte aneuploidy that frequently occurs with the maternal age. We found that in vivo supplementation of melatonin recovered its levels in the serum and follicular fluid that were decreased in aged female mice, and thus protected aged oocytes from meiotic defects and aneuploidy through Sirt1/Sod2-dependent mechanism.

A letter to the editor of Redox Biology by Dr. David J. Kennaway claimed that our observations regarding the improvement of oocyte quality caused by melatonin supplementation may be unsound because of 1) the low level of melatonin present in ICR mouse strain, 2) the accuracy of melatonin ELISA kit we used was not validated, and 3) the vehicle control for the melatonin and luzindole administration was not valid.

Firstly of all, we want to correct an unintentional mistake to the readers that the mouse strain used in this article was ICR (Institute of Cancer Research) rather than C57BL/6 in the original article. This can be evidenced by all our previous published papers, including a recent one involving the aging study [2]. In addition, we are confident about the data in our article because it has been verified by a recent independent investigation documenting that in vivo administration of melatonin was capable of alleviating the meiotic phenotypes of aged oocytes in ICR mice, specifically the spindle/chromosome disorganization and aneuploidy generation [3].

It has been reported long before that inbred strains of mice have a clear-cut circadian rhythm of pineal and serum melatonin [4]. C57BL/6 mice do produce melatonin in their pineal gland [5,6] with a small, but significant, peak in the middle of the darkness [7]. The low level does not deny its importance and functionality. Furthermore, besides the pineal gland, melatonin is produced by many other organs including ovary, testes, bone marrow, retina, gut, placenta, and liver [4,8]. Particularly, in the ovary, the granulosa cells, the cumulus oophorus, and the oocyte, along with the blood, may contribute melatonin to the follicular fluid, which has melatonin levels higher than those in the blood [9]. In humans, melatonin levels in the follicular fluid are positively correlated with the ovarian reserve and in vitro fertilization outcomes in women undergoing assisted reproductive technology procedures [10,11], and dramatically reduced in women of advanced reproductive age [12].

It is worth to note that previous studies have shown the presence of melatonin in the serum of ICR mice in the range of 80–100 pg/ml using an ELISA kit from IBL Germany [13] and 200–300 pg/ml using an ELISA kit from Shanghai, China [14]. More importantly, the study by Song et al. revealed that ~165 pg/ml of melatonin was detected (ELISA kit, IBL, Germany) in the young (2–3 months) Kunming strain mice (outbreed albino mice originated from the ICR strain), and demonstrated that long term supplementation with melatonin (10 mg/kg in drinking water for 12 months) increased the melatonin level from ~22 pg/ml in aged mice (14–15 months) to ~76 pg/ml and hence improved the age-induced fertility decline by counteracting ovarian mitochondrial dysfunction [15]. Consistent with above and other unlisted investigations, our results displayed that 100–120 pg/ml melatonin was detected in the serum of ICR mice using the ELISA kit from Beijing, China. Given that these data were generated from different labs using different kits, we think the variation range is reasonable.

Lastly, we injected PBS to aged mice as the control, and PBS containing melatonin and 10% ethanol (for dissolution of melatonin) as the rescue group. We believe one would not expect that it was not melatonin but ethanol that improved the quality of oocytes from the aged mice in the rescue group.

To sum up, stay tuned as more researchers will join in to validate our data and uncover the beneficial roles of melatonin in improving the low quality of mammalian oocytes induced by various causes.

Sincerely, Bo Xiong, Ph.D.

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https://doi.org/10.1016/j.redox.2020.101831
Received 14 November 2020; Accepted 4 December 2020
Available online 13 December 2020

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